

Maternal Beta HCG Levels Day 12 After Embryo Transfer to Predict Pregnancy Outcome in *In-vitro* Fertilization Clinic Prima Medika, Denpasar Bali Indonesia

IDA BAGUS MADE KARTHA¹, I MADE MAHADINATA PUTRA²,
IDA AYU INDIRA MANDINI² and I MADE PANDE DWIPAYANA³

¹Ob/gyn specialized, Reproductive Endocrinology and Infertility Consultant doctors in In-vitro Fertilization Clinic, Prima Medika Hospital, Denpasar, Bali, Indonesia.

²Ob/gyn specialized doctors, in In-vitro Fertilization Clinic, Prima Medika Hospital Denpasar, Bali, Indonesia.

³Division of Endocrinology and Metabolism, Department of Internal Medicine, Faculty of Medicine, Udayana University, Sanglah General Hospital, Denpasar, Bali, Indonesia.

*Corresponding author E-mail: dr.ibk_spog@yahoo.com

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ABSTRACT

Many methods to predict the outcome of pregnancies achieved after assisted reproductive technology (ART) has been tested. Several serum markers have been studied in relation to pregnancy outcomes, such as β -subunit of human chorionic gonadotropin (β -hCG), estradiol, progesterone, cancer antigen 125 (Ca-125), activins, and inhibin. Among them, β -hCG has been proven that the most predictive factor. Prediction of pregnancy outcome is important in an assisted reproductive technology program. Pregnancy obtained through IVF with or without ICSI have a higher risk of obstetric and perinatal complications compared with spontaneous pregnancies. To determine the clinical value of maternal serum β -hCG twelfth days after the embryo transfer and to predict pregnancy outcome. The method used was a retrospective study, in which the data was obtained from women undergoing IVF Clinic IVF Prima Medika Hospital Denpasar from January to December 2015. The non-viable pregnancy is defined as a biochemical pregnancy, ectopic pregnancy and miscarriage. Ongoing pregnancy is defined as a single pregnancy and multiple pregnancies, which reached more than a gestational age of 12 weeks. Serum β -hCG levels measured on the twelfth day after ovum pick up (OPU) and compared between the two groups Twelve days after embryo transfer, the mean levels of β -hCG in ongoing pregnancy group (419.7 ± 232.9 mIU/ml) was significantly higher than the group of non-viable pregnancies (44.8 ± 72.9 mIU/ml) ($p < 0.005$). In multiple pregnancies, the levels of β -hCG in multiple pregnancies (683.3 ± 194.4 mIU/ml) were significantly higher than singleton pregnancies (272.7 ± 155.0 mIU/ml) ($p < 0.005$). Levels of maternal serum β -hCG on the twelfth day after the embryo transfer has a good predictive value for assessing the clinical pregnancy outcomes in IVF program and helps to plan the subsequent follow-up.

Keywords: levels of beta hCG day 12, embryo transfer, prediction of pregnancy outcome.



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INTRODUCTION

The ability to predict the occurrence of pregnancy in the Assisted Reproductive Technology (ART) program is desirable both for the clinician and the patient. Some serum markers have been studied in relation to pregnancy, such as β -subunits from human chorionic gonadotropin (β -hCG), estradiol, progesterone, cancer antigen-125 (Ca-125), activin, and inhibin. β -hCG has proven to be the most predictive factor. Pregnancy obtained through IVF with or without ICSI has a high risk of obstetric and perinatal complications compared to spontaneous pregnancy.^{1,2,3} Ultrasound scanning is part of what is routinely done after embryo transfer, but the gestational sac can only be seen clearly during the third week after embryo transfer.^{4,5}

The success of embryo implantation, with invasion and proliferation of trophoblast cells, depends on endometrial receptivity. Estradiol (E2) is formed in the follicle, and the high number of pre-ovulatory follicles shows high E2 levels. Further affects the final oocyte maturation process with hCG in vitro fertilization (IVF), the supra-physiological formation of E2 and progesterone concentrations in the initial luteal phase, including the time of implantation. The high number of oocytes obtained during oocyte retrieval can lead to subsequent embryo-endometrial asynchrony affecting the embryo implantation process, resulting in less optimal trophoblast proliferation and low β -hCG levels.⁶

Table 1: Characteristics of Research Samples Based on Maternal- β -hCG Levels

Variables	Levels of β -hCG Maternal (mIU / mL)			
	Category	Mean	Standard Deviation	P
Maternal Age (Years)	23 – 33	357.9	276.7	0.206
	34 – 45	269.5	244.4	
Body Mass Index (BMI) (kg/m ²)	18 – 24	349.1	290.8	0.335
	> 24	281.0	232.9	
Infertile duration(Years)	1 – 10	324.9	268.2	0.086
	11 – 20	176.5	121.8	

Table 2: Mean of Maternal β -hCG Based Maternal Ratio Viability

Category	Variables	Levels of β -hCG Maternal (mIU / mL)		
		Mean	Standard Deviation	P
Category	Non-viable	44.8	72.9	0.000
	Biochemical Pregnancy	24.3	22.5	0.495
	Ectopic Pregnancy	70.5	-	
	Abortion	165.2	196.5	
	Ongoing pregnancy	419.7	232.9	0.000
	Single Pregnancy	272.7	155.0	0.000
	Twins Pregnancy	497.9	192.7	
	Multiple Pregnancy	683.3	194.4	

Table 3: Differences in Maternal-²-hCG Levels by Number of Fetuses

Variables	Category	Levels of β -hCG Maternal (mIU/mL)	
		Mean Diff.	P
Viable pregnancy	Single Pregnancy	410.56	0.004
	Multiple Pregnancy		
	Twin Pregnancy	185.44	0.283
	Multiple Pregnancy		
	Single Pregnancy	225.12	0.008
	Twin Pregnancy		

MATERIALS AND METHODS

In vitro fertilization clinic, Prima Medika Hospital Denpasar in January - Desember 2015, there are 138 participants who follow In-vitro Fertilization (IVF) program, with 123 participants who can follow up in the Ovum Pick Up (OPU) stage. Fifty-seven participants tested positive for biochemical pregnancy (46.3%) and 42 participants tested positive for clinical pregnancy (34.1%). The inclusion criteria is patient medical record data in Medical Record Unit of Prima Medika Hospital Denpasar, with positive biochemical pregnancy result after transfer of at least two embryo 8 cells. Levels of serum β -hCG were measured on the twelfth day after embryo transfer, at In vitro fertilization clinic, Prima Medika Hospital Denpasar, using immunoassay electroiluminesens method, measuring β -hCG levels to a minimum of <2.00 mIU/ml. Participants who tested positive for biochemical pregnancy were β -hCG > 10 mIU/mL. Of the 57 participants who had positive β -hCG levels, followed by 12 weeks' gestation, they were grouped into two major groups: viable pregnancies (ongoing pregnancy) and non-viable pregnancies (abortion, ectopic pregnancy, and biochemical pregnancy). Using an independent T-Test can detect the average difference in β -hCG levels between biochemical pregnancies, and abortion. The ANOVA (analysis of variance) test can determine the difference in mean β -hCG levels between single pregnancy, twin pregnancy, and multiple pregnancies, with 95% confidence intervals.⁷ As additional analysis, adjusted body mass index (BMI), maternal age and infertile duration. Statistical analysis was performed

with SPSS IBM Statistical Package version 17 for Windows with $p < 0.05$ being significant.

RESULTS AND DISCUSSION

The mean ²-hCG levels on day 12 after embryo transfer based on maternal age, body mass index and infertile duration. The mean β -hCG concentrations based on maternal age (23-33 years vs 34-45 years) were obtained (357.9 ± 276.7 vs 269.5 ± 244.4 mIU/mL), where the differences in both groups did not differ significantly statistically ($p = 0.206$). Based on body mass index (BMI), the sample with IMT 18-24 kg/m² was 349.1 ± 290.8 mIU/mL, while sample with IMT > 24 kg/m² was 281.0 ± 232.9 mIU/mL. Differences in both BMI groups showed no statistically significant ($p = 0.335$). Infertile duration between 1-10 years, the average β -hCG concentration was 324.9 ± 268.2 mIU/mL. The mean ²-hCG concentration in infertile 11-20 years was 176.5 ± 121.8 mIU/mL, where the difference between the two groups did not differ significantly ($p = 0.086$) (table 1). Sekhonm *et al.*, on observation of 458 patients who became pregnant after a single frozen embryo transfer (FET) transfer also found that maternal age factors did not differ significantly statistically.⁸ Similarly, in embryo or blastocyst transfer, the ²-hCG concentration in days 14 and 16 after OPU have no significant correlation with maternal age.⁹

The mean maternal β -hCG concentrations in the viable pregnancy were higher than non-viable pregnancies (419.7 vs 44.8 mIU/mL, $P = 0.000$). In non-viable pregnancies, for mean ²-hCG levels

in biochemical pregnancy was lower than abortion (24.3 vs 165.2 mIU/mL) but not statistically significant ($P = 0.495$). Wang *et al.*, in 212 IVF cycles received β -hCG 10 days after OPU differed significantly in both viable and non-viable pregnancies, as well as in single pregnancy and multiple pregnancy.¹⁰ Similarly, Reljic *et al.* found significantly different levels of β -hCG in both viable and non-viable pregnancies in the group of fresh embryo transfer and frozen embryo transfer examined on day 13 after embryo transfer.¹¹ The mean β -hCG concentrations in single pregnancies, twin pregnancies, and multiple pregnancies suggest a significant difference, as shown in Table 2.

In a viable pregnancy, the mean β -hCG concentrations in single pregnancies is smaller with twin pregnancies (gemelli) and is statistically significant ($p = 0.008$). The mean β -hCG levels of multiple pregnancies were greater than that of single pregnancies, which were statistically significant ($p = 0.004$). Meanwhile, the mean β -hCG concentrations in multiple pregnancies and twin pregnancies (gemelli) were different but not statistically ($p = 0.283$), as in Table 3.

Sing N, *et al.* on observation of median β -hCG levels on day 14 after transfer embryo,

found significant differences in median β -hCG concentrations in viable pregnancies (625 IU/L) and non-viable (174 IU/L), while median β -hCG levels singleton pregnancies (502 IU/L), twins (1093 IU/L) and triplets (2160 IU/L) were statistically significant.¹²

CONCLUSIONS

In this study there was a difference in mean β -hCG concentrations in viable pregnancies and non-viable pregnancies, with greater viable pregnancies. In single pregnancies, twin pregnancies and multiple pregnancies, there is a statistically significant difference.

In this study it was found that maternal β -hCG levels in very early pregnancy showed a significant difference based on viability. This finding has an effect on the interpretation of β -hCG levels after the ART program

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REFERENCES

1. Chen X, Huang Y, Guo PP, *et al.* The association between serum β -hCG on day 24 of pregnancy and ongoing pregnancy in frozen embryo transfer cycles. *International Journal of Gynecology and Obstetrics*. **134**: 278-281 (2016). Source Science Direct. Available from: <http://dx.doi.org/10.1016/j.ijgo.2016.02.019>
2. Basirat Z, Bijani A. Serum β -human chorionic gonadotropin levels at 16 days following embryo transfer in intra cytoplasmic sperm injection cycles to predict pregnancy outcome. *Saudi Medical Journal*. Source PubMed.; **31**:1015-1020 (2010). Available from:<http://www.researchgate.net/publication/46282173>
3. Jayachandran KD, Natarajan P, Pandiyan R. First Postembryo Transfer β -hCG Level and Pregnancy Outcome in an Assisted Reproductive Technology Program. *International Journal of Infertility and Fetal Medicine*. **3**: 57-62 (2012).
4. KIm JH, Shin MS, Yi G, *et al.* Serum biomarkers for predicting pregnancy outcome in women undergoing IVF: human chorionic gonadotropin, progesterone, and inhibin A level at 11 days post-ET. *Clin Exp Reprod Med.*; **39**: 28-32 (2012).
5. Zeadna A, Son WY, Moon JH, Dahan MH. A comparison of biochemical pregnancy rates between women who underwent IVF and fertile controls who conceived spontaneously. *Human Reproduction*. February 11, 2015; **0**: 1-6.
6. Tanbo TG, Eskild A. Maternal hCG concentrations in early IVF pregnancies: associations with number of cells in the Day

- 2 embryo and oocytes retrieved. *Human Reproduction* : 1-6.
7. Tumbelaka AR, Riono P, Sastroasmoro S, Wirjodiarjo M, Pudjiastuti P, Firman K. Bab 15 Pemilihan Uji Hipotesis. In:Sastroasmoro S, editor. Dasar-dasar Metodologi Penelitian Klinis. Jakarta: CV Sagung Seto; 2008. p.279-301.
 8. Sekhonm L, Rodriguez-Purata J, Aharon D, *et al.* Interpreting early HCG dynamics in the era of the thawed euploid single embryo transfer: how important is doubling? *Fertility and Sterility*. **106**(3): e341-e342 (2016).
 9. McCoy T.W, NakajimaST, Bohler Jr H C. Age and a single day-14 ²-HCG can predict ongoing pregnancy following IVF. *Reproductive BioMedicine*, **19**(1); 114-120 (2009).
 10. Wang Q, Zhang R, Jia M, *et al.* Serum beta-subunit human chorionic gonadotropin (²HCG) value could predict in vitro fertilization (IVF) pregnancy outcomes on the 10th day after oocytes retrieval. *Fertility and Sterility*.; **100**(3), pp.495 (2013).
 11. Relji M, Knez J, Vlaisavljevi V. Human chorionic gonadotropin levels are equally predictive for pregnancy outcome after fresh and vitrified-warmed blastocyst transfer. *Assisted Reproduction and Genetics*.; **30**(11); 1459–1463 (2013).
 12. Singh N, Begum AA, Malhotra N, *et al.* Role of early serum beta human chorionic gonadotropin measurement in predicting multiple pregnancy and pregnancy wastage in an in vitro ET fertilization cycle. *Human Reproductive Sciences*., **6**(3) ; 213-218 (2013).